New Diagnostic, Staging, and Therapeutic Aspects of Early Breast Cancer

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Many advances have occurred in breast cancer through research and clinical trials. More confidence in new biological consumptions about invasive breast cancer indicate that: (1) details of the primary breast cancer do not control survival; (2) breast-only failures after local excision do not bias against survival; and (3) cancer cell dissemination occurs at the same time via both lymphatic and hemotogenous routes. Early detection with mammographic screening has indicated a greater number of smaller breast cancers, including sharp increases in ductal carcinoma *in situ* (DCIS). With proper analysis and control, DCIS of limited extent can be treated by local excision with or without radiation. Invasive breast cancer of limited extent can frequently be managed by lumpectomy and radiation therapy with survival rates equivalent to the more traditional mastectomy. Patient desires regarding breast preservation and quality of life are paramount. Risk: benefit analyses for individual patients need to be emphasized in issues of breast preservation and in selecting adjuvant therapy, both regional (radiotherapy) and systemic (chemotherapy and hormonal therapy). We are entering an era of highly selective therapy based on more sophisticated analysis of the primary cancer. In the future, not only statistical predictions of outcome as achieved by flow cytometry, for example, will be more widely used, but individual prognostic factors may be developed such as with oncogene expression. Such individual prognostic factors will enable more selective therapy.
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IN NO FIELD OF CANCER TODAY is there such a wealth of investigation, both clinical and laboratory, as there is in breast cancer. This reflects the obvious emotional impact of a disease that arises in a prominent secondary sexual organ that has always represented beauty and femininity. It also reflects its frequency in young women, the clear epidemiologic relationship to diet and socioeconomic factors, the arrival of an effective technique of early detection, the development of breast-conserving therapy that is equally curative compared with mastectomy, increased curability by administration of adjuvant chemotherapy and hormonal therapy, and the improved palliation with multiple-agent chemotherapy or hormonal therapy without surgical ablation of endocrine organs.

What the woman wants to do with her breast has become the paramount decision point in the treatment of breast cancer. Thus, the woman's interest or lack of interest in maintaining her breast is what drives all the therapeutic decision making and the sequence of biopsies, the process of organizing information, the staging of the cancer, and the selection of the appropriate therapy for the patient. It is overwhelming to summarize the advances in breast cancer in a single article, and only a few highlights that represent the author's selective review of the large literature and his own attitudes about the care of patients with the disease are presented.

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Natural History and Biology

With the advent of public education campaigns in the late 1940s, median tumor size has progressively decreased at diagnosis, and the incidence of positive axillary lymph nodes likewise has declined.[1] Only in the past decade, however, have large numbers of nonpalpable breast cancers been discovered and treated. In the next decade it may well be that a majority of breast cancers will be detected in the preclinical stage by the use of widely applied screening mammography. What the natural history of such cancers would have been if untreated will probably always be speculative because mammographic detection in the United States today mandates therapy with few exceptions. However, a few retrospective studies of biopsy-only for what was, on later pathology slide review, determined to be microscopic foci of intraductal or lobular carcinoma in situ have indicated that a minority of such patients later develop evidence of invasive breast cancer.[2–5] Autopsy studies also indicate a significant incidence of breast cancer pathology including atypical ductal hyperplasia (ADH), duct carcinoma in situ (DCIS), lobular

carcinoma in situ (LCIS), and even small invasive carcinomas in women dying of other causes.[6,7] It is estimated that approximately 1% of patients with LCIS without a family history of breast cancer or ADH with a family history of breast cancer[8] will develop invasive cancer per year, which cumulatively will total approximately a 15% to 20% risk at 15 to 20 years.[2,4,5,8] Approximately 2% of patient with DCIS or LCIS with a family history of breast cancer will develop invasive breast cancer each year cumulatively totalling perhaps 30% to 40% at 15 to 20 years.[2-5] Data beyond that period of follow-up is sketchy but consistent with continuing risk of such magnitude.

Table 1 presents an estimate of subsequent risks of developing invasive carcinoma and an estimated risk of dying of breast cancer considering that 10% of cases followed in screening programs might die of disease, a high estimate. However, this presents an approximation of the extra risk of keeping a woman's breast in contrast to mastectomy that will serve as a useful discussion point for women with these diagnoses.

It is generally accepted now that lobular LCIS is a risk indicator of later invasive breast cancer rather than a true precursor lesion because the later invasive carcinomas that develop in follow-up may occur anywhere in the breast tissue.[2,9] In particular, one half of the subsequent cancers occur in the opposite breast and the cancers that occur in the ipsilateral breast are as likely to appear in other quadrants of the breast as the quadrant subjected to the biopsy. In contrast, DCIS when treated by biopsy-only results in later invasive cancers appearing in the same breast and in the same quadrant of that breast where the original biopsy was performed indicating that DCIS is a true precursor lesion in many patients.[4,5,10]

Of interest and consistent with its role as a marker of general risk of breast cancer, LCIS is more common in premenopausal women and is much less common in the postmenopausal years, especially in the elderly.[9] Thus, this lesion itself seems to disappear in time but leaves behind its mark of an increased risk in those patients where it has been encountered. It is not known where subsequent cancers occur after a diagnosis of atypical ductal hyperplasia.[8]

By extrapolating from a variety of studies, it appears that DCIS evolves slowly because the median age of focal DCIS is more than 5 years less than extensive DCIS,[11] and that in turn is less than the median age of invasive breast cancer.[12] Patients with DCIS and microinvasion are younger than patients with palpable invasive carcinoma with surrounding intraductal disease.

The implications of the finding that events early in life (*e.g.*, age of menarche, age at first childbirth, dietary patterns in the pre-adult life, and radiation in childhood) produce incidence patterns of breast cancer in late adulthood also are consistent with the assumption of a long natural history for the precursors of breast cancer and of breast cancer itself with causation of course being multifactorial. This cancer may well arise as a result of multiple separate factors, which each increases the probability of chromosomal mutation to a malignant clone of cells. Fox[13] proposed that human breast cancer consisted of at least two growth patterns and noted that the slow dying fraction of cases died at the rate of approximately 2.5% per year, whereas the rapidly dying population died at the rate of 25% per year with all such patients dying by 7 years. The rapidly dying fraction was thought to constitute perhaps 30% or more of all breast cancer patients. Clinically such a separation in growth pattern is recognized; patients having bad prognostic features are sometimes difficult to diagnose because of presentation with diffuse disease, negative mammograms, sometimes without a mass yet displaying extensive lymphatic permiation, multiple node metastases, and early dissemination and death. It would be of interest to learn whether adjuvant chemotherapy has a differential effect on this group of rapidly dying patients. It may well be that the effects of adjuvant therapy either hormonal or chemotherapeutic behave differently in these two growth patterns of the disease, but the *a priori* separation of patients into different growth patterns is not completely possible at present.

Discussion of breast cancer must recognize the rapidly improving clinical presentation, the currently undefined effect early presentation will have much later on age adjusted mortality rates, and the likelihood that from inception individual breast cancers may have strikingly different outcomes based on the interplay of host resistance factors and variations in inherent cancer cell aggressiveness. That not all hematogenously or lymphatically disseminated cancer cells lodge and/or grow as metastases is accepted. Cancer cell heterogeneity occurs such that cells from different cancers or different portions of a single cancer in a single host may have markedly different potentials for hematogenous or lymphatic spread, organ specific lodgement and growth, hormonal receptor content, hormonal sensitivity and response, chemotherapy

TABLE 1. Estimated Outcome in Patients With High-Risk, Noninvasive Breast Pathology Treated by Local Excision

Histology	Family history	Incidence of invasive cancer (%)		Estimated 20-year mortality rate if breast preserved
		Annually	After 20 yr	
ADH	No	0.5	10	1
	Yes	1	20	2
LCIS	No	1	20	2
	Yes	2	40	4
DCIS	No	2	40	4
	Yes	(4)	(60 at 15 yr)	(6)

ADH: atypical ductal hyperplasia; LCIS: lobular carcinoma in situ; DCIS: duct carcinoma in situ.

Values in parentheses are the authors' estimates; no other data are available.

response, production of angiogenesis compounds, many other features of cancer cell behavior, and histologic appearance.[14]

The understanding of the biologic behavior of breast cancer has completed a revolution in the past decade and began with breast cancer studies indicating that a variety of local treatments apparently produced similar end results in terms of cure.[15,16] This "new biology" is now widely accepted and has been most forcefully presented by Fisher and Wolmark[17] and is based on solid scientific data. In particular, the progressive clinical trials of the National Surgical Adjuvant Breast Program (NSABP), which because of their coherent overall plan of questions to be answered have provided comprehensive answers supports this new understanding of the biologic behavior in patients. Those trials and many other trials in other countries have illustrated and confirmed that a variety of effective local treatments ranging from local excision to total mastectomy to modified mastectomy (total mastectomy and partial axillary dissection) to radical mastectomy, performed with or without radiotherapy, provide equivalent survival rates. These studies can only be interpreted as indicating that the technical details of removing the primary cancer itself do not control survival, although local recurrence rates clearly are altered by features of the local primary cancer treatment.[17]

Lymph node metastases of small size that are not removed do not increase the risk of continuing dissemination and death.[14,17] Variations in lymph node removal or therapy (surgical removal, radiotherapy, or observation-only) result in exactly similar survival rates and confirm the fact that, like local recurrence after mastectomy, nodal metastases or nodal recurrences after axillary dissection or observation are "indicators but not governors" of survival[18] because survival is controlled by the disseminated cancer cells that grow as metastatic disease and destroy the host. The dissemination of these cells must have occurred before the removal of the primary cancer. Cell dissemination occurs by both lymphatic and hematogenous roots, but the ultimate pathway that carries cells to vital distant organs is hematogenous.

Lymph nodes are not millipore filters but undoubtedly are immunologic surveillance stations.[18] Cancer cells pass through and around lymph nodes and enter lymphaticovenous channels or directly enter blood vessels within the primary cancer. Some cancer cells may lodge and grow within lymph nodes, but these may be the minority and their lodgement does not lead to invariable progressive growth. Of particular interest in lymph node metastases is the fact that lymph node micrometastases less than 0.2 mm in diameter may have little relationship with decreased survival. Folkman[19] has shown that tumor masses cannot grow beyond approximately 2 mm in diameter without ingrowth of new blood vessels but can remain at that size or less for long periods with nutrition by diffusion only. Thus, lymph node micrometastases may be a clinical manifestation of viable but nonprogressive tumor nodules.

Prolongation of survival times and increases in cure rates will occur by killing or immobilizing the systemically disseminated cells and not by altering the details or extent of local primary cancer removal as long as reasonable local control is achieved.

This newer conceptual hypothesis or new biology is at considerable variance from the older one that implied that entrance to the vascular system occurred only after lodgement, progressive growth, and filling of the lymphatic channels and filtering lymph nodes with cancer cells; only then did cancer cells spill over to the more central blood vessels. This previous concept implied that the details and extent of local and regional tissue sacrifice made crucial differences in outcome. The new biology, most thoroughly documented in breast cancer, is nevertheless illustrated also in melanomas, sarcomas, and cancers of the lung, stomach, colon, liver, and other primary sites.

That breast cancer is a systemic disease from its acquisition of a blood vessel supply or that the dissemination of cells must occur extremely early in the natural progression from initial cellular origin to neovascularization by angiogenesis in a large proportion of cases is suggested by many studies.[14] Clinical reports indicate a high eventual rate of recurrence or metastases that continues exponentially with time and is displayed by the appearance of recurrent or metastatic disease even 30 or 40 years after mastectomy. Indeed, in Adair's 30-year follow-up,[20] only about 20% of patients were alive free of disease. A survey of deaths after mastectomy described a similar frequency of mortality rate, altered slightly by the increasing competing risks of older age.[21] The Fox study[13] implies an exponential death rate, which by definition never achieves a survival curve that is horizontal. These studies indicate that only by altering or killing the disseminated cells or altering the host response to these cells, perhaps by preventing angiogenesis and capillary ingrowth into micrometastases, can the actual cure rates be improved. The universally accepted role of systemic therapy as the treatment of disseminated cells is displayed in the profusion of trials of cytotoxic chemotherapy, hormonal or antiestrogen therapy, and the attempts at alternating host immunity.[22]

Early Detection

In the absence of sufficient knowledge to have acceptable and cost-effective preventive measures, early detection techniques are critical. Mammography was introduced less than 30 years ago and has gone through numerous technical advances that have reduced radiation dose, increased film quality, and provided dedicated radiograph machines so that now this radiologic examination is extremely safe, relatively inexpensive, and accurate. Sensitivity and specificity are relatively high, but because

most mammographic findings are nonspecific (such as calcifications and masses), total accuracy can never be achieved.[23] Mammograms performed in the presence of palpable, clinically definable cancers indicate false-negative rates of at least 5% to 10% or more. The false-negative rate of mammograms is unknown in nonpalpable cancers. The latter figure will become known only with more extensive and prolonged screening programs, which include a control group where the presence of a palpable cancer developing after multiple negative mammograms will be recorded over many subsequent years.

Several prospective trials of population screening with concurrent unscreened controls have been reported and analyzed beginning with the HIP study in New York City, which now has a prolonged follow-up.[24] Other controlled trials have been reported in Sweden,[25] Holland, and Italy, and ongoing trials are taking place in Canada, England, and Sweden. A large uncontrolled trial of the Breast Cancer Detection Demonstration Project (BCDDP) was performed in the United States.[23] These trial results can be summarized as indicating significant downstaging in screened women so that nonpalpable cancers are being detected frequently and, when physical examination is combined with mammography, palpable cancers are of earlier stage and have far fewer lymph nodes metastases. Reduction in deaths from breast cancer is significant in women older than the age of 50 years but still uncertain in women younger than the age of 50 years. The mortality rate reduction achieved amounts to 30% or more in these studies with early mortality rate reduction peaking at about 7 years in older women. Mortality rate reduction in younger women may not appear for many years beyond that, perhaps consistent with the prolonged natural history.[24] At present, clear evidence from population studies of the cost-effectiveness of mammographic screening in women younger than 50 years of age is questioned, and the contribution of the physical examination to the results of all screening programs in contrast to the use of mammography only is not completely clear but may be a major component of the advantages that are achieved.[26,27] The BCDDP[23] indicated that mammography could detect cancers in women between 40 and 49 years of age at a far higher rate than that seen with earlier mammographic techniques utilized in the HIP study. Thus, the question of utilization of screening mammography in women younger than the age of 50 years relates to the uncertain or delayed reduction in death rate, the lower incidence of the disease in that age decade, the large number of biopsies required for benign lesions detected on mammography, and the resultant high cost of each cancer detected and each life saved.[28]

When to stop routine screening of older women for breast cancer has not been explicitly addressed yet either, but the Swedish trial[25] found that women older than 75 years of age did not participate in the pro-offered trial, and thus may indicate a logical end point for routine screening in terms of general acceptance. Clearly, some age limit needs to be placed on population screening proposals because of the expense and the competing risks in older women, which reduce the importance of breast cancer as a threat to life. In addition, breast cancer in the elderly tends to be easier to detect because of decreased body weight, less prominent breast tissue, more frequent routine visits to physicians for general care, and the higher proportion of estrogen receptor rich cancers, which implies more successful treatment, better prognosis, and slower general cancer growth patterns. With the serious competing risks from aging and cardiovascular disease, a cutoff age of between 70 and 75 years would be logical for insurance coverage of costs. Thus, at present only broad outlines of the usefulness of breast cancer screening by mammography are available and more prolonged follow-up will be required to fully evaluate its impact on prognosis and survival and mortality rates.[28]

More studies still need to be performed with untreated or unscreened control groups to complete our understanding of the usefulness and cost-effectiveness of mammography in contrast to physical examination in various age groups.[29] The cost-effectiveness of screening programs at various ages needs continued study. Programs of single-view mammograms conducted by technicians with mass reading of films by trained nonphysicians will be more cost-effective but difficult to conduct in this country because of patient expectations and the legal climate, which imposes serious restraints by threats of legal actions for programs that have inherent inaccuracies. At present the majority of patients still present with self-discovered palpable breast cancers, but that proportion will decrease progressively as wider application of screening mammograms occurs, although programs in minorities and socioeconomically disadvantaged groups may continue to lag without specific public policy directions.

Noninvasive Breast Cancer

Noninfiltrative carcinomas (DCIS and LCIS) now make up between 20% and 50% of all biopsies performed because of mammographic abnormalities without physical findings.[30] Indeed, in recent reports noninvasive carcinomas may constitute as many as 10% of all breast cancers recorded in some institutions in contrast to only 1% to 3% of cases before nonpalpable lesions were routinely screened for and biopsied.[12]

The natural history of noninvasive cancers is still uncertain because large numbers of cases have only been detected in the past decade. As noted previously, however, it is currently accepted that LCIS is not a precursor lesion for invasive breast cancer but a risk indicator, with subsequent cancers arising anywhere in breast tissue.[2,9] DCIS is thought to be a precursor lesion for the most part with

subsequent cancers appearing in the same breast in the same quadrant after treatment by biopsy only.[4,5,10]

Incomplete understanding of the course and nature of DCIS does not prevent rapid changes in attitude resulting from investigations of its therapy. The studies of most pertinence in addressing the issue of contemporary therapy are those of Lagios *et al.*[11,31] In 115 DCIS diagnosed by mammographic screening or palpation of a mass, biopsy, and subsequent mastectomy and axillary dissection, Lagios *et al.*[11,31] performed whole-organ step sections and mammograms and then pathologic examinations of any abnormal specimen mammographic findings; on empirical grounds they found that patients with DCIS less than 2.5 cm in diameter had a median diameter of 8 mm, only 14% multicentricity, no occult invasion, and no node metastases. In contrast, patients with DCIS greater than 2.5 cm in diameter had a median diameter of 5.6 cm, a 54% incidence of multicentricity, a 46% incidence of occult invasion, and a 4% incidence of node metastases. The median age of the smaller group was 53 years and 58 years for the latter, larger group. It is difficult to escape the conclusion that many small DCIS lesions led in time to the latter large lesions by means of ductal spread and that only later in the disease course did apparent multicentricity and invasion through the basement membrane into surrounding periductal tissues arise. The only real test of this hypothesis of ductal spread from a solitary focus to create multicentricity is to treat the smaller lesions by local excision alone and observe the long-term outcome. To make the study even more pertinent, 62% of the small DCIS in the report by Lagios *et al.*[11,31] were detected by mammogram only and 17% were incidental lesions, whereas 63% of the larger DCIS were detected by physical examination. Thus, the smaller lesions correspond to the DCIS now being discovered in mammographic screening programs and the larger lesions correspond to the palpable DCIS seen in previous decades and frequently classified as comedo carcinoma.

Subsequently, Lagios *et al.* have treated 79 patients with calcification-identified, mammographically discovered DCIS of less than 2.5 cm in greatest diameter by local excision only.[31,32] Eleven (14%) of these patients have recurred in the breast after a median follow-up of 4 years, of which five recurrences were invasive and six were DCIS.[32] Schnitt *et al.*[10] analyzed the 595 total patients reported in several series with mastectomy or breast preserving therapy for DCIS; all but Lagios' series were performed for palpable masses, however; 323 patients had mastectomy with only 2 (0.6%) local recurrences, but a few patients did die of disease. One hundred seventy-nine patients had local excision and radiotherapy with a 6% local recurrence and two patients (1%) died of disease. Twenty-two patients had local excision only without radiotherapy with a 23% recurrence rate but no deaths from disease. The Lagios *et al.* study[31] is the only one reported with nonpalpable DCIS treated with local excision and thus fulls a critical role in evaluating the kind of therapy required for managing patients with DCIS discovered in screening mammograms. Other guidelines[10,33] for consideration of local excision-only as a treatment option are reproduced in Table 2.

TABLE 2. Guidelines for the Evaluation of Patients With Mammographically Detected, Nonpalpable Lesions With Microcalcifications, Being Considered for Breast-Conserving Treatment

1. Careful mammographic evaluation of the breast before biopsy, including magnification views, to delineate the extent of the microcalcifications
2. Needle localization for the biopsy
3. Specimen radiography, preferably with magnification views and contact views, to confirm that the lesion has been excised and to direct pathologic sampling
4. Careful gross description of the excised specimen by the pathologist
5. Inking of the specimen margins by the pathologist before sectioning, to facilitate evaluation of margins on permanent sections
6. On microscopic examination description of the relation of the calcifications to the lesion and the distance of the tumor from the inked margins of resection
7. Postbiopsy mammography with magnification views to confirm that all suspicious microcalcifications have been removed
8. Repeat excision of the primary site if residual microcalcifications are seen on postbiopsy mammography or if tumor involves margins of resection microscopically

Data from Schnitt *et al.*[10]

For DCIS lesions greater than 5 cm in diameter or with positive margins after reexcision, or with multifocal disease, or other suspicious calcification in the ipsilateral breast by mammography, mastectomy should be performed. Lesions between 2.5 cm and 5 cm in diameter with clear margins after excision, with or without a focal area of microinvasion, can be considered for local excision, perhaps followed by radiotherapy[10] if mastectomy is not desired.

A guideline for future risk of developing invasive breast cancer and the possibility of dying of such cancers if the original high-risk noninvasive pathology was treated by local excision only and the patient was followed closely is given in Table 1. This table extrapolates from data available as cited[2-10] and the survival results of patients participating in breast screening programs.[23]

Any patient undergoing local excision for DCIS at present with or without radiotherapy needs to be fully informed about the risks of recurrence and the small possibility of metastases. These patients need to understand they have embarked on a nonstandard therapy, but many such women are happy to select such an option to keep their breasts as long as the surgeon is able to follow the patients carefully with both frequent physical examinations and mammograms. Both surgeon and patient must be aware of the still uncertain outcome of such a program. A reasonable practice is to examine such patients every

3 or 4 months with mammograms every 6 months for the first 2 years; prompt biopsy of any suspicious findings or possible recurrence must be performed during follow-up (Table 1).

A recent article[33A] demonstrating overexpression of the neu oncogene in the subset of DCIS with large cell comedo pathologic type associated with progressive growth illustrates the possibility for future precise separation of microfoci DCIS into the potentially invasive *versus* those of no clinical importance.

Unilateral mastectomy for LCIS is illogical. Treatment options include biopsy or local excision-only with careful follow-up by both mammogram and physical examination or bilateral mastectomy. Because the risk of subsequent invasive cancer in patients with LCIS and a premenopausal family history is much higher than those without such a family history, the marker lesion of LCIS should lead to a discussion of the possibility of bilateral mastectomy for attempted prevention of subsequent cancer. Some women in such families are, appropriately, extremely fearful of breast cancer and are relieved by the removal of both breasts, with reconstruction if desired in an attempt to prevent breast cancer. Reconstruction by subpectoral implants seems to be the most reasonable cosmetic recovery because of the continued exposure to physical examination of the mastectomy bed for surveillance. Cancers have been reported to develop in the residual fragments of breast tissue that remain even after complete mastectomy, and local recurrences do occur.[34]

Table 1 provides a useful estimate of the patient's maximum risk of dying of breast cancer by selecting breast preservation instead of mastectomy (or bilateral mastectomy) for therapy of marker or preinvasive lesions.

The hope of population screening by mammogram and accompanying physical examination is to have the majority of cancers appear in a preinvasive stage of small size with the realization that perhaps 50% or more of such focal tiny DCIS lesions would never progress to a clinical cancer with invasion. The effect of such DCIS and LCIS lesions, which were never slated to recur or progress to clinical cancer being detected, classified as cancer, and treated, on statistical evaluations of incidence and survival in breast cancer, will require sophisticated interpretation of breast cancer data in the future. The crude result analysis will suggest an increase in the apparent incidence of cancer and improvement in the overall cure rate.

Invasive Breast Cancer of Limited Extent

These cancers correspond to Stage I (T1a and T1b) of the current AJC-UICC staging system[35] and are now being seen with increasing frequency because of breast cancer screening programs detecting nonpalpable small cancers. The BCDDP, for instance,[30] found that 16% of invasive cancers with measured size were 1 cm or less in diameter when detected by the screening procedure, and 12% of their interval cancers were also less than 1 cm in diameter. Such cases also include DCIS with microinvasion. The BCDDP recorded survival rates in these patients of 97% at 8 years in women 40 to 49 years of age and 98% at 8 years for women 50 to 59 years of age.[23] The overall 20-year survival of patients with palpable invasive cancers less than 1 cm at Memorial Hospital first seen in the years 1940 to 1943 was 77%.[36] The incidence of lymph node metastasis in patients with invasive cancer less than 1 cm in diameter is approximately 20% in the survey of the American College of Surgeons[12] and node-positive patients that have other than micrometastases may have sharply reduced survival expectation. Rosen *et al.*[37,38] noted only 14% positive nodes in patients with invasive cancers that were palpable but were 1 cm or less in diameter. However, the incidence of lymph node metastases in nonpalpable invasive cancers less than 1 cm discovered by mammography only is only 9%.[30] Fisher *et al.* reported[39] that about two thirds of patients with less than 1 cm invasive cancers with positive nodes have only one to three node metastases; many of those will be only micrometastases.

These early breast cancers are being detected with increasing frequency, and even with a few axillary metastases or micrometastases have an excellent prognosis; consideration should be given for an even more conservative approach than has been utilized for invasive breast cancer generally in the past decade. Therapeutic directions for future consideration in this group of women are the use of local excision-only after ascertaining that excision margins are clear, without the use of radiotherapy.[40] In the NSABP trial, B-06,[41] local recurrence in patients with lesions up to 4 cm in diameter subjected to local excision-only was 32%, and a recurrence after such lumpectomy and the addition of radiation therapy was approximately 7%. Local recurrence after lumpectomy without radiation therapy was associated with size over 2 cm, poor histologic grade, poor nuclear grade, or lymphatic permeation, implying that for selected small invasive cancers, local breast recurrence was uncommon. For patients in the trial with lesions less than 1 cm, the local recurrence rate with lumpectomy-only was less than 15% and with lumpectomy and radiation was about 7%.[42] Thus, the addition of radiotherapy was of relatively less usefulness in these small cancers. Lagios *et al.*[43] found two recurrences (18%) after local excision only of 11 invasive cancers less than 1.0 cm in diameter.

Although the concept of lumpectomy, axillary dissection, and radiation therapy is accepted as a standard therapy for patients with T1 and T2 primary cancers up to 4 cm in diameter following the protocol of NSABP B-06, local excision or lumpectomy without radiation therapy is considered nonstandard therapy despite the failure to demonstrate any adverse effect on survival in the NSABP

protocol B-06 followed for 8 years. The still more conservative option of avoidance of radiotherapy in selected small primary cancers needs to be considered in the context of a clinical trial but without a trial available may be chosen on an ad hoc basis with selected patients who are well informed and willing to accept some implied risks of local recurrence.

There may also be consideration of avoidance of axillary dissection in such small selected cancers. For instance, whereas 20% of palpable invasive cancers less than 1 cm in diameter have positive nodes[12] only 9% of nonpalpable cancers less than 1 cm in diameter detected by mammography have positive lymph nodes,[30] and as many as 40% of these are only micrometastases[44] as noted previously.

The potential reduction in mortality rates by performing axillary dissections for staging in cancers less than 1 cm in diameter and instituting adjuvant therapy may be only 20% (postoperative tamoxifen therapy in ER-positive, node-positive, postmenopausal women) to 25% (postoperative chemotherapy in node-positive, premenopausal patients)[45] in the 10% to 20% of patients with positive lymph nodes. In premenopausal patients (25% of breast cancer) with 20% incidence of positive nodes and a 25% reduction in mortality rates, only 2.5% of patients overall might have an improved outcome. In postmenopausal patients the gains would be less and equal at most to 2%. For such a gain, axillary dissections are done in every patient and require hospitalization and general anesthesia, postoperative shoulder rehabilitation, and produces at least a 15% incidence of arm edema, although usually of minor extent. If the incidence of positive lymph nodes decreases as the incidence of nonpalpable mammographically detected primary breast cancers increases and their size decreases, avoidance of axillary dissection may become acceptable in selected subgroups of patients. Axillary sampling rather than axillary dissection may be a conservative variation in these patients, particularly because such procedures might be performed under local anaesthesia as an outpatient. If adjuvant therapy will eventually be given to all patients, regardless of axillary node status, axillary dissection will have no role in therapy selection, and alternatives in staging requirements may be necessary.

Therapy for Stage I and Stage II Breast Cancer

There is complete acceptance now of the concept that Stage I breast cancer can be treated with breast conservation with equivalent survival in appropriate cases compared with mastectomy.[17] The selection factors for such breast-conserving surgery are disputed at present, with some surgeons arguing that few if any women should have a mastectomy and others arguing that only a minority of patients should have retention of the breast. The prime factor that should drive all decision making about breast conservation is the patient's: does the patient wish to preserve her breast and is she willing to go through the several separate steps required to achieve that? The patient's desire should be the prime motivating force in these options. It is just as wrong to insist that a patient accept lumpectomy when she does not want it as it is to insist on mastectomy when the patient desires breast preservation. Some young women suitable for lumpectomy strongly desire a mastectomy but cannot get their local surgeon to perform it, and some women strongly desire breast preservation but their surgeons will not even discuss that option.

There should be several criteria for ready acceptance of lumpectomy and radiation therapy in the treatment of early primary breast cancer:

1. Patient desire.
2. Appropriate cancer size to breast size ratio: a large cancer in a small breast treated by lumpectomy may create a poor cosmetic result. However, the eventual cosmetic result frequently cannot be predicted without performing the lumpectomy and observing the cosmetic result after a short period of time. Patients are far less critical of the cosmetic outcome after lumpectomy and radiation therapy than radiotherapists and surgeons. Frequently a less than satisfactory or even poor cosmetic outcome is acceptable to the patient. Thus, physicians need to be flexible in making decisions about appropriate therapy of the breast cancer, with the patient's attitudes and desires incorporated into the decision making process.
3. Absence of extensive intraductal cancer (EIC) within and surrounding the invasive cancer.[46,46A] Such patients have a high (35% at 8 years) local breast recurrence rate and therefore are less suitable for breast conservation. However, patients with EIC but negative excision margins may decide that a 65% chance of preserving their breasts without an apparent significant risk of decreased survival is an acceptable alternative and choose lumpectomy and radiation therapy despite recommendations against it. In these situations as long as explanations are carefully given and patients are fully aware of the risks and recommendations for mastectomy, we are willing to treat patients with lumpectomy and radiation therapy. Intelligent and informed patients are critical participants and usually will select mastectomy if recommended, perhaps with reconstruction. In these situations the surgeon should maintain continued interest and guidance and perform the surgery if the patient seems willing to assume the risks after complete comprehension of the issues.
4. Unifocal breast cancer or two cancer foci close enough together so that a single boost field to a limited area of the breast can be utilized for adequate local control. Although Fisher *et al.*[41] advocate 5000 cGy without local boost fields, a reduced total breast dose of approximately 4500 cGy and a local boost with elections to maximize

local control by the addition of approximately 1600 cGy is recommended.[47]

5. Careful and detailed follow-up must be performed because frequent breast examination and mammograms after lumpectomy with or without radiation is an essential part of the therapeutic program to detect possible local recurrences. Recurrences should be treated by mastectomy usually,[48,49] but additional segmental resection is sometimes possible.[50]

Utilizing these criteria two thirds of patients or more may achieve breast preservation. Approximately 30% of patients have EIC,[46] but some are accepted for breast conservation if the cancers are small and excision margins are clear. Approximately 10% of patients desire mastectomy regardless of their suitability for lumpectomy for a variety of personal, geographic, or convenience reasons, and approximately 5% of patients have either an inappropriate size ratio of breast cancer to breast, or extensive noninvasive DCIS. The usual treatment sequence is as follows:

1. Initial office visit. Aspiration biopsy if a mass is palpable; arrangement for localization mammogram and biopsy if the lesion is nonpalpable; arrangement for outpatient local anaesthesia lumpectomy.

2. Lumpectomy under local anaesthesia as an outpatient either for a palpable mass or a localized nonpalpable mass or calcification after localization mammogram. Frozen section and estrogen receptor if the mass can be palpated in the specimen; tiny invasive or in situ cancers do not require ER determinations because the test may be inaccurate and may destroy tissue essential for determining the extent of disease and the subtleties of microinvasion. India ink application to the surface of the lumpectomy specimen is essential for pathologic evaluation of the adequacy of tissue removal. It is as critical to manage the breast specimen appropriately as it is to manage the breast cancer patient appropriately.

3. Review of the situation with patient and family to discuss options in light of the biopsy-lumpectomy cosmetic results, the final pathology report with evaluation of EIC, size, invasiveness of the cancer, and evaluation of the tissue margins. A rereview of the patient's desire regarding breast conservation or mastectomy is important after judging the cosmetic appearance following lumpectomy. A final decision for or against lumpectomy can be made at this time. Discussion about the patient's desire for reconstruction if mastectomy is either required or desired in consultation with a plastic surgeon can be obtained at this point.

4. Consultation with the radiotherapist for patients undergoing lumpectomy.

5. Admission to hospital for general anaesthesia to perform an axillary dissection if lumpectomy is chosen or for mastectomy and axillary dissection with or without immediate reconstruction.

6. Consultation with the medical oncologist for patients with positive axillary nodes or with poor prognostic features if nodes are negative.

Follow-up procedures utilized after primary therapy differ considerably between mastectomy and lumpectomy patients. After mastectomy patient follow-up can be focused on the return of shoulder motion by vigorous exercises and six monthly operative site evaluations for 2 years and then less frequently with a mammogram of the opposite breast once per year. If adjuvant therapy is utilized, laboratory tests need to be considered at intervals, but bone scans and radiologic tests on a routine basis without symptoms are to be discouraged.[51,52] Following lumpectomy and breast conservation, however, three monthly detailed breast physical examinations need to be performed for at least 2 years with less frequent examinations for the next 3 years and then yearly examinations after 5 years because local failure is then less common. A mammogram is obtained every 6 months for the first 2 years and then yearly with particular attention to the lumpectomy site. Mammograms may suggest recurrence initially because of stellate scarring. Any suggestion of a thickening or mass in the primary lumpectomy site should be biopsied either by aspiration cytology or true-cut needle biopsy at frequent intervals because evaluation of the local site with scarring, irradiation, fibrosis, and thickening is sometimes extremely perplexing and clinically uncertain. Shoulder function is also emphasized if axillary dissection was performed.

If chest wall recurrences appear after mastectomy, full diagnostic workup frequently reveals systemic disease; if the disease is localized, local measures are utilized. If breast tissue recurrence appears after lumpectomy, however, the implications are far different. Search for systemic metastases is performed, but recurrence within the breast tissue itself does not carry the implication of systemic disease that recurrence in the chest wall after mastectomy implies.[48-50] Therefore, the option of local reexcision can be considered in selected patients with large breasts, small localized recurrence, no EIC, a strong desire to retain the breast, and no evidence of systemic disease. However, standard therapy for breast recurrence after lumpectomy and radiation therapy should be mastectomy, which frequently requires plastic surgical reconstruction with transferred flaps of skin and muscle because of the less satisfactory skin elasticity and skin flaps that can be created in the radiated breast.

Quality of Life

Satisfactory cosmetic outcome can be achieved in the vast majority of patients with lumpectomy and radiation therapy.[53] These results were evaluated by physicians, and

patients tend to be more satisfied with the retained breast despite degrees of distortion, edema, shrinkage, skin changes, or other abnormalities that would be more critically evaluated by surgeons and radiotherapists. Only 15% to 20% of patients had a fair or poor cosmetic appearance by physician evaluation. Factors that were associated with less satisfactory cosmetic appearance were larger volume of tissue removed, reexcision of a previous biopsy, implant techniques of radiotherapy locally (now largely abandoned), radiotherapy techniques that include additional nodal drainage basin irradiation rather than two tangents only to the breast tissue itself, and the simultaneous use of adjuvant chemotherapy. The local excision should be performed through skin lines of minimal tension, relatively centrally in the breast, without cautery on the specimen itself, without drainage, and with attention to cosmetic appearance.

Axillary dissection should be performed with cosmetic and functional objectives in mind when combined with lumpectomy. A separate, horizontal incision should be used in the lower axilla, below the axillary hairline. It is critical to remove level I and the portion of level II lymph nodes up to the midpectoralis minor muscle, but it is equally important to not strip clean the axillary vein and to protect the lateral pectoral nerve for pectoral muscle innervation. The lateral pectoral nerve courses around the lateral border of the pectoralis minor muscle and enters the posterior surface of the pectoralis major muscle and can always be spared by careful dissection. Some authors sacrifice the pectoralis minor muscle in an attempt to take the entire axillary contents in which case the nerve is greatly endangered if not routinely sacrificed. Sacrifice of this muscle is not required to obtain adequate staging axillary dissection because skip metastases to the axillary apex are uncommon.[54] Obviously, the long thoracic and thoracordorsal nerves need to be identified carefully and preserved.

The brachiocutaneous sensory nerve can be preserved by careful dissection, but this is not commonly performed because its branches within the axilla have a variable course, are small, and are entirely sensory. The sensory defect that results from nerve sacrifice is bothersome but not disabling and generally recovers within a few months, although this recovery is delayed for many months if radiation therapy is utilized. Arm edema may occur after axillary dissection and radiation therapy. Its occurrence can be minimized by not stripping the axillary vein and avoiding axillary radiotherapy.[55]

The avoidance of axillary dissection would be another significant step forward in achieving a more satisfactory cosmetic result because subsequent breast and arm edema occur with some frequency, and shoulder dysfunction is almost entirely a consequence of the axillary dissection.

Women feel better socially, emotionally, and sexually after breast conservation than after mastectomy,[56] and they are better emotionally with reconstruction than after mastectomy alone particularly if the reconstruction is immediate.[57] Thus, when mastectomy is selected by the patients or necessitated by the clinical or pathologic features, patients should be offered reconstruction by some sort of plastic surgical procedure. Two issues regarding plastic surgery are currently under analysis. The first is the timing of the reconstruction, whether immediate or delayed, whereas the other is whether to use expandable subpectoral implants or pedicle myocutaneous flaps from abdominal or latisimus dorsi areas.[58] These two issues are somewhat interrelated because the addition of the time and blood loss by the pedicle flap techniques to the mastectomy creates a major operative procedure. Thus, for immediate reconstruction, most plastic surgeons today perform a subpectoral expandable implant, which adds little to the operative trauma or time and gives satisfactory cosmetic results. When mastectomy is performed for recurrence after lumpectomy and radiation therapy, however, a pedicle flap is frequently required because of lack of elasticity of the skin flaps or radiotherapeutic skin damage that might interfere with healing and the inability to use skin expanders subpectorally because of the skin stiffness and pressure and inability to obtain skin stretching with implant distention. The use of pedicle flaps in such a situation can create an extremely satisfactory cosmetic appearance but requires immediate rather than delayed reconstruction.

Prognostic Factors

Continuing analysis of subgroups of breast cancer patients is critical for quality of life because the possibility of increased conservation of tissue and preservation of breasts will be permitted by more careful delineation of risk factors for local recurrence and the continued trends toward smaller cancers. Similarly better prognostication for cure and survival will permit more women to live longer after appropriate adjuvant therapy.

Axillary metastases remain the most widely applicable and reliable prognostic feature. Axillary dissection should be performed in most patients because judgments about adjuvant therapy are made on the basis of nodal metastases. When reliable and widely applicable prognostication can be made by flow cytometry, thymidine labeling index, genetic analysis of the cells, oncogene analysis, and estimations of host resistance or other biochemical techniques, axillary dissection may become unnecessary. Furthermore, if all patients will eventually be treated by adjuvant therapy regardless of nodal status, axillary dissection may become obsolete and used only for progressive, palpable axillary nodal disease.

A recent review of prognostic features summarizes the

current status of these important tests.[59] Estrogen receptor (ER) and particularly progesterone receptor (PR) status is considered to be of prognostic importance, although not all reports agree. There is an indication that the combination of ER and PR values are important so that if both ER and PR are positive, the prognosis is better than if the ER is positive but the PR is negative. If both ER and PR are negative, prognosis is clearly worse. The level of PR may be related to prognosis so that values more than 50 fmol connote significantly better prognosis than values between 5 and 49 fmol. Such a separation may not be apparent in ER levels, however, but because most PR values are related to the ER values, there may be interrelationships prognostically.[59]

Thymidine labeling index (TLI) of cells has been shown to be significantly correlated with outcome because it is a measurement of the proliferative thrust of the breast cancer cells.[60] However, the test is time-consuming, complicated, expensive, and requires tissue culture of fresh cancer cells. It may never come into widespread usage. TLI is significantly correlated with ER and PR so that a high labeling index is associated with ER and PR negativity.

Flow cytometry is an increasingly useful technique to measure cell proliferative rate and is more widely applicable, but still expensive and not widely available.[61] This technology will undoubtedly become more extensively utilized and can even be done on formalin-preserved tissue. The technique detects abnormal DNA content of cells. Patients with a high aneuploid cell population have more axillary lymph node metastases. Within the population of patients with aneuploid tumors, subgroups with hypodiploid and hypertetraploid cells have a particularly poor outcome. The potential clinical applicability of flow cytometry is great and it may well become a routine measurement of prognostic importance in the years to come. Currently, no prospective trials utilize flow cytometry as a discriminant for selecting adjunctive chemotherapy or hormonal therapy, but its importance as a clinical prognostic tool may promote such usefulness in the near future.

Analysis of oncogenes in cancers is entering a new research phase and may also prove to be of clinical usefulness in the future.[33A] Increased gene amplifications or deletions may be related to increased recurrence rates, through accelerated neoplastic growth or removal of suppressor factors. Such studies will require far more research and clinical correlation before becoming clinically useful. Host reactivity to autologous breast cancer by a skin window technique[62] has correlations with outcome. That host immunity has correlation with prognosis has been emphasized by the higher mortality rate after transfusions given with mastectomy[63] because of the impact of transfused leukocyte cells on immune tolerance.

Detailed pathologic and histologic criteria, such as nuclear grade, lymphatic permeation, and poor differentiation, continue to be subjects of review. Unfortunately, none of these criteria nor any of the aforementioned prognostic indicators are totally reliable or discriminating for outcome, and thus currently no accepted standard has been widely accepted except axillary lymph node metastases.

The need for precise and reliable prognostic indicators is critical to rationalize our therapy in the future, particularly in patients without axillary metastases. Such tests would enable adjuvant therapy to be selected for patients slated to recur, whereas patients with an excellent prognosis might be spared toxic or prolonged therapy. Precise cytogenetic markers would play a critical role in evaluating members of familial groups, for instance, because patients destined to develop a cancer could be reliably defined, as in Huntington's chorea. The relief of anxiety in patients defined as being free of future risk of breast cancer would be a marked gain. Selected family members destined to develop cancer could embark on preventative therapy rationally. We can expect marked progress in these research endeavors in the near future.

Progress in Staging

The most important development in staging has been an adoption of a universal system by the American Joint Committee (AJC) and the International Union Against Cancer (UICC) so that not only is a highly sophisticated staging system available, but it is utilized throughout the world.[35] In particular, the TNM system now permits separate classification of small cancers that are becoming more frequently detected by mammography screening programs. T1a defines cancers 0.5 cm or less in greatest diameter and T1b as primary cancers more than 0.5 cm but not larger than 1 cm in diameter. T1c defines cancers between 1 and 2 cm in diameter. Recognizing that the median diameter of breast cancers in the United States today is less than 2 cm in maximum diameter, it is critical to have this more elaborate subset staging available for more sophisticated analysis. In addition, node metastases are separated in more precise categories. N1a node metastases are micrometastases less than 0.2 mm in diameter. N1b1 patients have one to three lymph node metastases larger than 0.2 mm (more than micrometastases) but less than 2 cm in diameter. N1b3 node metastases have extension through the node capsule but are less than 2 cm in overall diameter.

With the increases in precise staging, more reliable comparisons between different therapies may be made and therapy made more precise. In addition, more detailed biologic understanding of various subgroups of small quantity disease will enable greater understanding of the

behavior of breast cancer. It is apparent that the selection of breast cancer treatment will become even more complicated in the future with a wide selection of options for extent of tissue removal, types of adjuvant therapies, and extent of and need for radiation therapy. This more elaborate, contemporary staging system will promote and codify such therapeutic systems.

The development of monoclonal antibodies to a variety of breast cancer antigens is another area of great research interest with the potential for use in selecting prognostic groups and precise staging by discovering occult bone marrow metastases and even for use in precise therapy of metastatic disease if the antibodies can be complexed with radioactive substances or toxic chemicals.[64] This entire field has recently been reviewed by Thor *et al.*[65]

Adjuvant Therapy

There is no longer controversy regarding use of adjuvant therapy in node-positive or poor prognostic breast cancer.[45] There is still controversy, however, about what constitutes poor prognosis besides lymph node metastases because, for instance, ER-negative cancers in some series do not carry a clearly worse prognosis.[59] Furthermore, the more contemporary studies of thymidine labeling index and flow cytometry are not widely available and cytogenetic analysis is still a research tool. The usual poor prognostic features continue to be large size and lymph node metastases. However, even within groups of patients, precise individual prognostication is not possible; for instance, T3N0M0 patients have a relatively good prognosis and have been placed in Stage II in the most recent AJC-UICC staging classification, and many patients with positive lymph nodes survive without adjunctive therapy. In addition, adjuvant therapy is not universally successful, and even when given in maximal doses for prolonged periods may only yield a 25% to 33% reduction in mortality rates in premenopausal women with multidrug chemotherapy and a 20% reduction in mortality rate in postmenopausal women with tamoxifen.[45,66] A host of technically correct scientific, clinical studies have been completed or are under way, which indicate variations of the theme of adjuvant therapy of presumed micrometastatic disease. These studies include chemotherapy and hormonal therapy separately or in combination and study a variety of drugs and a variety of cyclic applications of combinations of drugs in alternating non-cross-resistant chemotherapy combinations. Progestational agents and anti-estrogenic tamoxifen and oophorectomy are all under study and review. The field is so complex that it is nearly impossible to summarize, but Abeloff and Beveridge[45] review the progress made since the 1985 consensus development conference on adjuvant therapy. The article indicates that no dramatic differences in the results presented or summarized at that meeting have occurred. Clearly, clinical trials need to continue because they provide some substantial advances in both biologic understanding and survival in many patients. However, numerous controversies cannot yet be resolved, but overall guidelines in adjuvant therapy studies in the future are given in a commentary by Carbone[67] in his discussion of the article by Abeloff and Beveridge:

> Thus, the messages I would like to articulate are as follows: 1) continue to accrue patients to well designed adjunctive high dose chemotherapy trials, 2) look for ideas that test concepts rather than variations, 3) do not put all of our resources into one mega trial. Develop an overall strategy in the disease that will take into account other than treatment approaches, such as early detection, epidemiology, and prevention, 4) encourage studies that have laboratory components that might answer biologic questions as well as treatment choices. 5) remember that all current management approaches are half way technologies along the way to finding important biological principles that point to specific ways to prevent disease or control its manifestations before major expressions of organ damage occur. That has been the history of all disease control. The salves, ointments, potents, leeches, fulgerations, and extirpative operations have all given way to modern specific approaches that prevent or control disease with minimal interference with organ function. Accumulation of basic biologic knowledge rapidly defines the correct ultimate approach, leaving behind to be forgotten all the old remedies.

Most recently, new controversy and debate arose in response to a "clinical alert" released by the National Cancer Institute.[68,69] This clinical alert suggested that most node-negative breast cancer patients should be treated with adjuvant therapy beginning even 3 years after the primary cancer treatment. The trials on which the alert was based indicate some improvement in disease-free survival but do not yet indicate an improvement in overall survival of patients compared with untreated controls.[66] Whether such reductions in early recurrence will later translate into a gain in overall survival is completely unknown at the present time but is implied by trials in node-positive women. The nature of the information dissemination via the public press, the fact that the clinical alert was based on studies not yet published, and the fact that recommendations did not discriminate by stage of disease was unfortunate and caused much anguish among patients and the oncologic community.[68,69] The bypassing of traditional avenues of defining newer therapeutic strategies through professional debate and discussion in scientific journals and meetings or by the convocation of a consensus conference has created unnecessary controversy. Currently, it is unclear which node-negative patients should

be treated with adjuvant therapy, but it is clear that a balance of risks and benefits is required. Thus, a postmenopausal woman with a 7 mm invasive cancer detected by mammography with a better than 95% chance of cure certainly may not wish to take adjuvant tamoxifen, even though toxicity is low, because the gain in survival is barely measurable (mortality rate reduced from 5% to 4%[70]). However, a premenopausal woman with a palpable 3 cm invasive cancer of the breast with negative nodes would probably gladly accept the chemotoxicity for a presumed 25% to 33% reduction in mortality rate.[66]

Participation in clinical studies should be encouraged for all physicians and surgeons managing breast cancer patients, and among patients with breast cancer, for such trials are critical for progress. Based on data currently available, the following broad guidelines for adjuvant therapy seem reasonable:

1. Adjuvant radiotherapy after mastectomy seldom needs to be utilized. Only in thoughtfully selected individual patients will it provide significant help in preventing local chest wall recurrence. Adjuvant radiation therapy of regional lymph nodes should not be performed after mastectomy or axillary dissection even if lymph node metastases are present because nodal or axillary space recurrences are uncommon, do not impair survival opportunities, and can be treated when they occur.

2. Adjuvant plastic surgical procedures should be offered to all patients undergoing mastectomy either immediately at the time of mastectomy or later in the follow-up period. Immediate reconstruction seems to provide real gains in emotional well being and recovery without interfering with later adjuvant chemotherapy or detection of chest wall recurrences.

3. Multidrug chemotherapy should be offered to all premenopausal women with axillary lymph node metastases indicating a high likelihood of recurrence. Such therapy should also be considered in perimenopausal women. Many different combinations of drugs exist, and balances need to be established between toxicity and effectiveness.

4. Tamoxifen anti-estrogen therapy should be offered to all postmenopausal women with axillary metastases and ER or PR-rich cancers. Some trials indicate that these benefits may accrue to ER-negative patients also and such therapy should be considered.

5. Multidrug chemotherapy in premenopausal women and tamoxifen in postmenopausal women should be considered in node-negative women with poor prognostic features, recognizing that so far improvements in overall survival have not been reported, although disease-free survival is improved. The degree of improvement is approximately 20% reduction in postmenopausal women with tamoxifen and 25% reduction in premenopausal women with polychemotherapy.

6. Definition of "poor prognostic features" is a value judgment to be determined by the patient with guidance by the surgeon, medical oncologist, and primary physician. Clear appreciation of the risk–benefit ratios is required for decisions to be made.

7. In all other situations participation in ongoing trials to understand the possible benefits of adjunctive therapy are to be strongly encouraged; routine use of these treatments is discouraged.

Prevention

Prevention of breast cancer in high-risk groups or even large populations would be of enormous importance. In two large trials comparing adjuvant tamoxifen with untreated controls, results indicate a reduction in new opposite breast carcinomas in women after mastectomy. A specific chemoprevention trial is currently under way in England and one trial in breast cancer is currently sponsored by the National Cancer Institute evaluating 4-hydroxyphenyl retinamide.

Jordan[70] has reviewed his own and others extensive animal model experiments utilizing tamoxifen and clinical use, which indicates its tumorostatic or suppressor action that would indicate long periods of administration for prevention activity. Toxicity is extremely low.

Conclusions

Marked changes in the therapy of breast cancer have occurred in the past decade, and there is every indication that continued alterations in management will evolve in the years ahead. The trend to discover and exploit newer technologies and approaches will undoubtedly accelerate if the changes of the past are projected into the future. Predictions of routine therapy even 5 years in the future are uncertain. The need for more precise subset prognostication is great so that individualization of therapy may be achieved. Noninvasive and early invasive cancers are being encountered more frequently as screening mammography is becoming more common, and these cancers may well lend themselves to still more conservative therapy if current trends continue.

Major concerns about the economic costs of screening large numbers of women for detection of relatively few cancers exist. In addition, widespread application of expensive adjuvant chemotherapy to large groups of women at relatively less overall risk of death may alter the cost–benefit ratio of these treatments also, emphasizing the critical need for accurate reliable prognostic indicators.

REFERENCES

1. Cady B. Changing patterns of breast cancer. *Arch Surg* 1972; 104: 266–269.

2. Haagensen CD, Lane N, Lattes R, Bodian C. Lobular neoplasia (so-called lobular carcinoma in situ) of the breast. *Cancer* 1978; 42:737–769.

3. Farrow JH. Current concepts in the detection and treatment of the earliest of the early breast cancers. *Cancer* 1970; 25:468–477.
4. Betsill WL, Rosen PP, Lieberman PH *et al.* Intraductal carcinoma: Long-term follow-up after treatment by biopsy alone. *JAMA* 1978; 239: 1863–1867.
5. Page D, Dupont WD, Rogers LW, Landerberger M. Intraductal carcinoma of the breast: Follow-up after biopsy only. *Cancer* 1982; 49: 751–758.
6. Bartow SA, Pathak DR, Black WC, Key CR, Teaf SR. Prevalence of benign, atypical, and malignant breast lesions in populations at different risk for breast cancer. *Cancer* 1987; 60:2751–2760.
7. Neilsen M, Jensen J, Andersen J. Precancerous and cancerous breast lesions during lifetime and at autopsy. *Cancer* 1984; 54:612–615.
8. Dupont WD, Page DL. Risk factors for breast cancer in women with proliferative breast disease. *N Engl J Med* 1985; 312:146–151.
9. Frykberg ER, Santiago F, Betsill WL Jr, O'Brien RH. Lobular carcinoma in situ of the breast. *Surg Gynecol Obstet* 1987; 164:285–299.
10. Schnitt SJ, Silen W, Sadowsky NL, Connolly JL, Harris JR. Current concepts, ductal carcinoma in situ (intraductal carcinoma) of the breast. *N Engl J Med* 1988; 318:898–902.
11. Lagios MD, Westdahl PR, Margolin FR, Rose MR. Duct carcinoma in situ: Relationship of extent of noninvasive disease to the frequency of occult invasion, multicentricity, lymph node metastases, and short-term treatment failures. *Cancer* 1982; 50:1309–1314.
12. Bedwani R, Vana J, Rosner D, Schmitz RL, Murphy GP. Management and survival of female patients with "minimal" breast cancer: As observed in the long-term and short-term surveys of the American College of Surgeons. *Cancer* 1981; 47:2769–2778.
13. Fox MS. On the diagnosis and treatment of breast cancer. *JAMA* 1979; 241:489–494.
14. Fidler IJ, Balch CM. The biology of cancer metastasis and implications for therapy. *Curr Probl Surg* 1987; 24:137–209.
15. Yarbro JW. The new biology. *Semin Oncol* 1985; 12:55–56.
16. Carbone PP, Tormey DC. The clinical investigator and the evolution of the treatment of primary breast cancer. *Semin Oncol* 1986; 13: 415–424.
17. Fisher B, Wolmark N. Conservative surgery: The American experience. *Semin Oncol* 1986; 13:425–433.
18. Cady B. Lymph node metastases: Indicators, but not governors of survival. *Arch Surg* 1984; 119:1067–1072.
19. Folkman J. Angiogenesis: Inititation and modulation. In: Nicolson GL, Milas L, eds. Cancer Invasion and Metastasis: Biologic and Therapeutic Aspects. New York: Raven Press, 1984; 201–209.
20. Adair F, Berg J, Joubert L, Robbins GF. Long-term follow-up of breast cancer patients: The 30-year report. *Cancer* 1984; 33:1145–1150.
21. Mueller CB, Jeffries W. Cancer of the breast: Its outcome as measured by the rate of dying and causes of death. *Ann Surg* 1975; 182:334–339.
22. Henderson IC, Hayes DF, Come S, Harris JR, Canellos G. New agents and new medical treatments for advanced breast cancer. *Semin Oncol* 1987; 14:34–64.
23. Seidman H, Gelb SK, Silverberg E, LaVerda N, Lubera JA. Survival experience in the breast cancer detection demonstration project. *CA* 1987; 37:258–290.
24. Shapiro S, Venet W, Strax P *et al.* Ten-to-fourteen-year effect of screening on breast cancer mortality. *JNCI* 1982; 69:349–355.
25. Tabar L, Gad A, Holmberg LH *et al.* Reduction in mortality from breast cancer after mass screening with mammography. *Lancet* 1985; 1: 829–832.
26. Tabar L, Dean PB. The control of breast cancer through mammography screening. What is the evidence? *Radiol Clin North Am* 1987; 25:993–1004.
27. Lung JA, Hart NE, Woodbury R. An overview and critical analysis of breast cancer screening. *Arch Surg* 1988; 123:833–838.
28. Wright CJ. Breast cancer screening: A different look at the evidence. *Surgery* 1986; 100:594–598.
29. Proceedings of the Workshop on Strategies to Lower the Costs of Screening Mammography-1986. American Cancer Society. *Cancer* 1987; (Suppl) 60:1669–1702.
30. Baker E. Breast cancer detection demonstration project: Five-year summary report. *CA* 1982; 32:194–225.
31. Lagios MD, Margolin FR, Westdahl PR, Rose MR. Mammographically detected duct carcinoma in situ: Frequency of local recurrence following tylectomy and prognostic effect of nuclear grade on local recurrence. *Cancer* 1989; 63:618–624.
32. Lagios MD. Personal communication. 1989.
33. Lagios MD. Human breast precancer: Current status. *Cancer Surv* 1983; 2:383–402.
33A. Van de Vijver MJ, Peterse JL, Wolter JM *et al.* Neu-protein overexpression in breast cancer, association with comedo-type ductal carcinoma in situ and limited prognostic value in stage II breast cancer. *N Engl J Med* 1988; 319:1239–1245.
34. Feller WF, Holt R, Spear S, Little JW. Modified radical mastectomy with immediate breast reconstruction. *Ann Surg* 1986; 52:129–133.
35. Beahrs O. American Joint Committee on Cancer: Manual for Staging of Cancer, ed. 3. Philadelphia: JB Lippincott, 1988.
36. Berg JW, Robbins GF. Factors influencing short and long term survival of breast cancer patients. *Surg Gynecol Obstet* 1966; 122:1311–1316.
37. Rosen PP, Saigo PE, Braun DW, Weathers E, Kinne DW. Prognosis in Stage II ($T_1N_1M_0$) breast cancer. *Ann Surg* 1981; 194:578–584.
38. Rosen PP, Saigo PE, Braun DW Jr, Weathers E, DePalo A. Predictors of recurrence in stage I ($T_1N_0M_0$) breast carcinoma. *Ann Surg* 1981; 193:15–25.
39. Fisher B, Bauer M, Wickerham L *et al.* Relation of number of positive axillary nodes to the prognosis of patients with primary breast cancer—an NSABP update. *Cancer* 1983; 52:1551.
40. Ghossein NA, Vilcog J, Stacey P, Asselain B. Is it necessary to irradiate the breast after conservative surgery for localized cancer? *Arch Surg* 1987; 122:913–917.
41. Fisher B, Bauer M, Margolese R *et al.* Five-year results of a randomized clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. *N Engl J Med* 1985; 312:665–673.
42. Redmond C. Personal communication. 1988.
43. Lagios MD, Richards VE, Rose MR, Yee E. Segmental mastectomy without radiotherapy: Short-term follow-up. *Cancer* 1983; 52:2173–2179.
44. Rosen PP, Saigo PE, Braun DW, Weathers E, Fracchia AA, Kinne DW. Axillary micro- and macrometastases in breast cancer, prognostic significance of tumor size. *Ann Surg* 1981; 194:585–591.
45. Abeloff MD, Beveridge RA. Adjuvant chemotherapy of breast cancer: The consensus development conference revisited. *Oncology* 1988; 2:21–26.
46. Osteen RT, Connolly JT, Recht A, Silver B, Schnitt SJ, Harris JR. Identification of patients at high risk for local recurrence after conservative surgery and radiation therapy for stage I or II breast cancer. *Arch Surg* 1987; 122:1248–1252.
46A. Rosen PR, Kinne DW, Lesser M, Hellman S. Are prognostic factors for local control of breast cancer treated by primary radiotherapy significant for patients treated by mastectomy? *Cancer* 1986; 57:1415–1420.
47. Harris J, Hellman S. Conservative surgery and radiotherapy. In: Harris J, ed. Breast Diseases. Philadelphia: JB Lippincott, 1987; 299–324.
48. Recht A, Schnitt SJ, Connolly JL *et al.* Prognosis following local or regional recurrence after conservative surgery and radiotherapy for early stage breast carcinoma. *Int J Radiat Oncol Biol Phys* 1989; 16:3–9.
49. Kurtz JM, Amalric R, Brandone H, Aymer Y, Spitalier JM. Results of salvage surgery for mammary recurrence following breast-conserving therapy. *Ann Surg* 1988; 207:347–351.
50. Kurtz JM, Amalric R, Brandone H, Aymer Y, Spitalier JM. Results of wide excision for mammary recurrence after breast-conserving therapy. *Cancer* 1988; 61:1969–1972.
51. Zwaveling A, Albers GHR, Felthuis W, Hermans J. An evaluation of routine follow-up for detection of breast cancer recurrences. *J Surg Oncol* 1987; 34:194–197.
52. Tomin R, Donegan WL. Screening for recurrent breast cancer: Its effectiveness and prognostic value. *J Clin Oncol* 1987; 5:62–67.
53. Rose MA, Olivotto IA, Cady B *et al.* The long-term cosmetic results of conservative surgery and radiation therapy for early breast cancer. *Arch Surg* 1989; 2:153–157.
54. Schwartz GF, D'Ugo DM, Rosenberg AL. Extent of axillary dis-

section preceding irradiation for carcinoma of the breast. *Arch Surg* 1986; 121:1395–1398.

55. Larson D, Weinstein M, Goldberg I *et al.* Edema of the arm as a function of the extent of axillary surgery in patients with stage I–II carcinoma of the breast treated with primary radiotherapy. *Int J Radiat Oncol Biol Phys* 1986; 12:1575–1582.

56. Kemeny MM, Wellisch DK, Schain WS. Psychosocial outcome in a randomized surgical trial for treatment of primary breast cancer. *Cancer* 1988; 62:1231–1237.

57. Schiain WS, Wellisch DK, Pasnau RO *et al.* The sooner the better: A study of psychological factors in women undergoing immediate *versus* delayed breast reconstruction. *Am J Psychol* 1985; 142:40–46.

58. Hartrampf CR Jr, Bennett GK. Autogenous tissue reconstruction in the mastectomy patient: A critical review of 300 patients. *Ann Surg* 1987; 205:508–519.

59. Clark GM, McGuire WL. Steroid receptors and other prognostic factors in primary breast cancer. *Semin Oncol* 1988; 15:20–25.

60. Silvestrini R, Daidone MG, DiFronzo G, Morabito A, Valagussa P, Bonadonna G. Prognostic implication of labeling index versus estrogen receptors and tumor size in node-negative breast cancer. *Breast Cancer Res Treat* 7:161–169.

61. Dressler LG, Seamer LG, Owens MA, Clark GM, McGuire WL. DNA flow cytometry and prognostic factors in 1331 frozen breast cancer specimens. *Cancer* 1988; 61:420–427.

62. Black MM, Zachrau RE, Hankey BF, Wesley M. Skin window reactivity to autologous breast cancer: An index of prognostically significant cell-mediated immunity. *Cancer* 1988; 62:72–83.

63. Wu HS, Little AG. Perioperative blood transfusions and cancer recurrence. *J Clin Oncol* 1988; 6:1348–1354.

64. Schlimok G, Funke I, Holzmann B *et al.* Micrometastatic cancer cells in bone marrow: In vitro detection with anti-cytokeratin and in vivo labeling with anti-17-1A monoclonal antibodies. *Proc Natl Acad Sci USA* 1987; 84:8672–8676.

65. Thor A, Weeks MO, Schlom J. Monoclonal antibodies and breast cancer. *Semin Oncol* 1986; 13:393–401.

66. Henderson *et al.* Effects of adjuvant tamoxifen and of cytotoxic therapy on mortality in early breast cancer: An overview of 61 randomized trials among 28,896 women. *N Engl J Med* 1988; 319:1682–1692.

67. Carbone PP. The article reviewed. *Oncology* 1988; 2:30–32.

68. Spratt JS. The National Cancer Institute's clinical alert on breast cancer: Why the hurry? *Am J Surg* 1988; 156:153–154.

69. Balch CM. Adjuvant therapy for node-negative breast cancer patients: Who benefits? *Arch Surg* 1988; 123:1189–1190.

70. Jordan VC, ed. Estrogen/Antiestrogen Action and Breast Cancer Therapy. Madison: University of Wisconsin Press, 1986.